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(54) Title: (-)-[[4-(1,4,5,6-TETRAHYDRO-4-METHYL-6-OXO-3-PYRIDAZINYL)PHENYL]-HYDRAZONO]PROPANE-DINITRILE

(57) Abstract

Optically substantially pure (-) enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or pharmaceutically acceptable salt thereof, intermediates and a process for the preparation are described. The product is useful as a cardiotonic agent, antihypertensive and vasodilator for the treatment of congestive heart failure.

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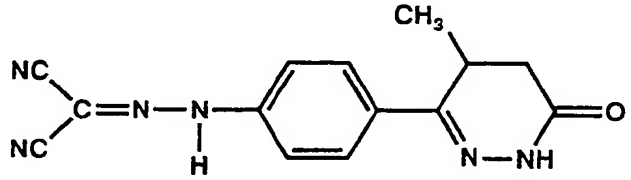
(-)-[[4-(1,4,5,6-TETRAHYDRO-4-METHYL-6-OXO-3-PYRIDAZINYL)PHENYL]-HYDRAZONO]PROPANEDINITRILE

The present invention relates to the pure (-) enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile of formula



I

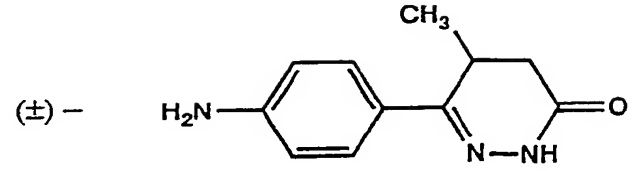
The invention also relates to salts, compositions and a process for the preparation of this enantiomer as well as to new intermediates of this process.

The compound according to the invention is useful as cardiotonic agent, antihypertensive and vasodilator for the treatment of congestive heart failure.

The racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) with melting point of 258-263°C has been described earlier in applicant's patent application GB 2228004. It was shown that the compound (I) is potent in the treatment of congestive heart failure and has significant calcium dependent binding to troponin. Our further studies have now unexpectedly revealed that the cardiotonic potency is predominantly due to the optically active (-) enantiomer of this compound. Furthermore it was found that the water solubility of the (-) enantiomer is over 30 fold compared to the racemate. The bioavailability of the (-) enantiomer was also found to be superior compared to racemate. Therefore the pure (-) enantiomer is especially suitable over the racemic compound to be used as a medicament for treating congestive heart failure.

The (+) and (-) enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) can be separated by passage of the racemic compound over a chiral phase chromatography column. However, this method is tedious if larger amounts of material is needed.

Another possibility to obtain the pure enantiomers of compound (I) is the use of corresponding optically active enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one as an intermediate. The racemic 6-(4-amino-phenyl)-5-methyl-pyridazin-3(2H)one of formula (II)

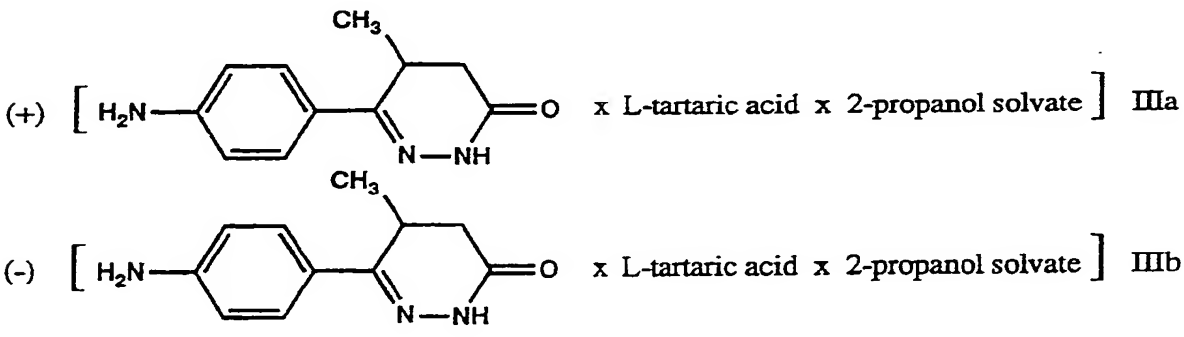


II

can be synthesized by methods known in the literature (J. Med. Chem., 17, 273-281 (1974)). The resolution of the racemic compound (II) has, however, been proved very difficult because the 4-amino group in the molecule is weakly basic. The salts of 6-(4-amino-phenyl)-5-methylpyridazin-3(2H)one with optically active acids hydrolyse on crystallization readily back to the compound (II) and to the resolving compound which interfere the resolution procedure or make it totally impossible.

The separation of the pure enantiomers of compound (II) on a chiral HPLC-column has been described in European patent application EP 208518. This method is, however, not applicable for industrial scale. An enantio-selective seven step synthesis of (-)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one starting from (+)-2-chloropropionic acid has also been described in the literature (J. Org.Chem., 56, 1963 (1991)). The total yield in this method is only 12 % giving (-)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one with an optical purity of 97.2 %.

It was now found that good enantiomeric separation of compound (II) could be obtained by using L- or D-tartaric acid in excess, preferably about 2 to about 3 equivalents, to the compound (II) in 2-propanol. The acid salts of (-)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one with L-tartaric acid 2-propanol solvate (IIIb) or corresponding (+)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one with D-tartaric acid 2-propanol solvate (IIIa) crystallize in good yield and in practical optical purity.



IIIa

IIIb

It was further found that the minor component in a partly enriched

enantiomer mixture may be crystallized out as racemic compound (II) from dioxane leaving the rest of the major component in the solution. Thus the salts (IIIa) or (IIIb) obtained in the crystallization mentioned above were filtered and the free base was liberated with potassium carbonate solution and the product were treated with dioxane. Both enantiomers of (I) are thus obtained by this two phase crystallization procedure in high optical purity of over 99 %. The yield in this process is also very good, because the rasemic compound (I) is obtained from dioxane in crystalline state and may be recycled. Both resolving compounds L- or D-tartaric may be alternatively used in the above process, but the natural L-tartaric acid is preferable because it is much cheaper.

The optically substantially pure (-) and (+) enantiomers of the compound (I) may then be prepared from the corresponding optically substantially pure (-) and (+) enantiomer of compound (II), respectively, by the usual process disclosed in applicant's patent application GB 2228004, in high optical purity and in nearly quantitative yields. The process described in GB 2228004 for preparing the compound (I) comprises treating the compound of formula (II) with sodium nitrite and malononitrile in acidic conditions. The term "optically substantially pure" means here optical purity over about 90 %, preferably over 95 % and more preferably over 99 %.

Salts of the enantiomers of compound (I) may be prepared by known methods. Pharmaceutically acceptable salts are useful as active medicaments, however, preferred are the salts with alkali or alkaline earth metals.

Solubility

TABLE 1.

The water solubility of (-) enantiomer and racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) in 67 mM phosphate buffer (pH 2).

Compound	Solubility (mg/ml)
(-) enantiomer	0.029
racemic	0.0007

Cardiotonic action

Cardiotonic action of the (-) and (+) enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) was studied in isolated, electrically paced, right ventricular papillary muscle of guinea-pig. Experiments were carried out in normal Tyrode's bath solution as described by Otani et al., Japan. J. Pharmacol. 45, 425, 1987.

The results are presented in Table 2. They show that the (-) enantiomer was 47 times more potent than the (+) enantiomer.

TABLE 2.

Cardiotonic effects of the (-) and (+) enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile in guinea-pig papillary muscle.

Enantiomer	EC_{50}, mM
(-)	0.06
(+)	2.8

Bioavailability

Concentration of total [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile in dog plasma after single dose oral administration of the racemate (1 mg/kg) and (-)-enantiomer (0.5 mg/kg) is shown in Figure 1. Curve A is for the (-)-enantiomer and curve B is for the racemic [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile. The figure shows that when (-)-enantiomer is used instead of the racemate less than half dose is needed to produce the same plasma concentration level of the total drug substance.

The pharmaceutically active compound according to this invention is formulated into dosage forms using the principles known in the art. It is given to mammalian organisms, i.e., humans, a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, dragees, capsules,

suppositories, emulsions, suspensions or solutions. The composition according to the invention contains an therapeutically effective amount of the pharmaceutically active compound of the invention. The contents of the active compound is in the composition from about 0.5 to 100 % per weight. In general, the compound of the invention may be administered to man in oral doses as low as ranging from about 1 to 50 mg per day. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used. The LD_{50} value of the (-) enantiomer given intravenously to rats was 57 mg/kg.

The compositions are formulated depending upon the purpose of the medicine, normal uncoated tablets being quite satisfactory. Sometimes it is advisable to use coated tablets, i.e. so-called enterotablets, to secure that the medicine reaches the desired part of the gastrointestinal tract. Dragees and capsules may be used too.

Example 1

Resolution of racemic 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one with L-tartaric acid.

(±)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one (203 g, 1 mole) was dissolved in 2-propanol (40 dm^3) on heating. To this solution (L)-tartaric acid (300 g, 2 mole) was gradually added. The mixture was stirred on heating until a clear solution was obtained. The solution was cooled slowly to room temperature with stirring. After it has been stirred over night at 20°C the crystalline product (IIIb) was filtered. The wet salt was dissolved in water (1.5 dm^3) and potassium carbonate solution (190 g K_2CO_3 in 0.75 dm^3 of water) was added with stirring. The free base was filtered, washed with water and dried. The product (104.6 g) was dissolved in dioxane (0.6 dm^3) on heating and allowed to cool to room temperature. The racemic 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one was filtered (74.6g) and the filtrate was evaporated to dryness in vacuo yielding (-)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one as a crystalline solid (23.8 g) with optical purity of 99.5 %, m.p. 207 - 210°C, $[a]_D^{25}$ = -383° (ethanol-water-conc. HCl 17:2:1).

The 2-propanol solution containing the (+)-enantiomer together with the racemate of compound (I) was evaporated to dryness in vacuo. The residue was treated with potassium carbonate solution as described above to give a mixture of (+)-enantiomer and racemate (87.3 g) which was dissolved on heating in dioxane (0.48 dm^3). The racemate was filtrated after cooling (48.0 g) and the filtrate was evaporated to dryness in vacuo yielding (+)-6-(4-amino-phenyl)-5-methylpyridazin-3(2H)one as a crystalline solid (26.1g) with optical purity of 99.5 %, mp. 206 - 209°C, $[a]_D^{25}$ = +391° (ethanol-water-conc. HCl 17:2:1). In total 122.6 g of racemate was recovered. The yield of (-)-enantiomer of (I) was thus 59.2 % and the yield of (+)-enantiomer of (I) 64.9 %.

Example 2

(+)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-propanedinitrile

The title compound was prepared as described in patent application GB 2228004 from (+)-6-(4-amino-phenyl)-5-methylpyridazin-3(2H)one. Yield 98 %, mp 210-214°C , $[a]_D^{25}$= 568° (tetrahydrofurane-methanol 1:1).

Example 3.

(-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-propanedinitrile

The title compound was obtained as described above from (-)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one. Yield 97 %, mp 210-214°C, $[a]_D^{25}$= -566° (tetrahydrofurane-methanol 1:1).

Example 4.

Preparation of pure diastereomeric salt (IIIa)

508 mg (2.5 mmol) of pure (+)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one obtained in Example 1 was dissolved in 100 ml of 2-propanol. 750 mg (5.0 mmol) of D-tartaric acid was added and the mixture was heated to boiling. On cooling 800 mg of crystalline (+)-6-(4-aminophenyl)5-methyl-pyridazin-3(2H)one D-tartrate mono 2-propanol solvate was obtained, mp. 97-105°C.

Example 5

Preparation of pure diastereomeric salt (IIIb)

The above process was repeated by using (-)-6-(4-amino-phenyl)-5-methylpyridazin-3(2H)one and L-tartaric acid. Mp. 98-106°C.

Example 6

Preparation of (-)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one by resolution of the corresponding racemate with L-tartaric acid.

(±)-6-(4-aminophenyl)-5-methylpyridazin-3(2H)one (203 g, 1 mole) was dissolved in 2-propanol (10 dm^3) on heating. To this solution (L)-tartaric acid (300 g, 2 mole) was gradually added. The mixture was stirred on heating until a clear solution was obtained and cooled slowly during 3 h to 50°C and stirred further over night at 50°C. The crystalline product was filtered and the procedure described in Example 1 was repeated. The yield of (-)-6-(4-amino-phenyl)-5-methylpyridazin-3(2H)one was 30.3 g (97.4 % of the theoretical). The optical purity was 99.7 %. In total 140.8 g of the racemate was recovered.

The optical purities of the compounds were determined by the high performance liquid chromatography. The instrument was a Waters 600 E gradient pump with a Waters 991 photodiode array detector and a Waters 700 Satellite Wisp injector (Millipore Co.) controlled by a NEC Powermate SX Plus computer. The enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one were separated by using a sellulose-type chiral column (Chiracel =OJ, 4.6x250 mm, Daicel Chemical Industries LTD.). The mobile phase consisted of 97 % 2-propanol and 3 % hexane. The flow rate was 0.3 ml/min. The enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-propanedinitrile were separated by using a ß-cyclodextrin column (Cyclobond Ib, 4.6x250 mm, Advance Separation Technologies Inc.). The mobile phase consisted of 41 % methanol in water buffered to pH 4.0 with 1 % triethyl-ammonium acetate. The flow rate was 0.3 ml/min.

Claims

1. (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile and pharmaceutically acceptable salts thereof.

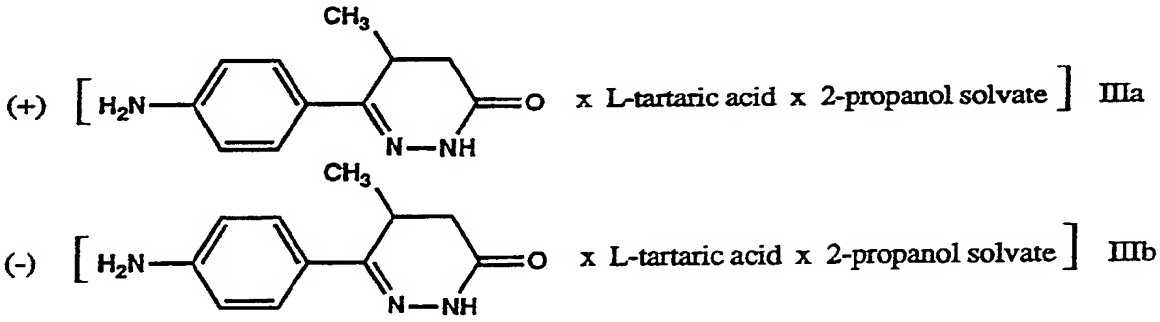
2. A pharmaceutical composition which comprises a therapeutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

3. A process for the optical resolution of (±)-6-(4-aminophenyl)-5-methyl-pyridazin-3(2H)one, which process comprises contacting the mixture of enantiomers with L- or D-tartaric acid in 2-propanol, recovering the resulting crystalline salt and optionally basifying the salt to form the corresponding free base.

4. A process as claimed in claim 3, wherein the free base is further dissolved in dioxane and the filtrate containing the optically active free base is recovered.

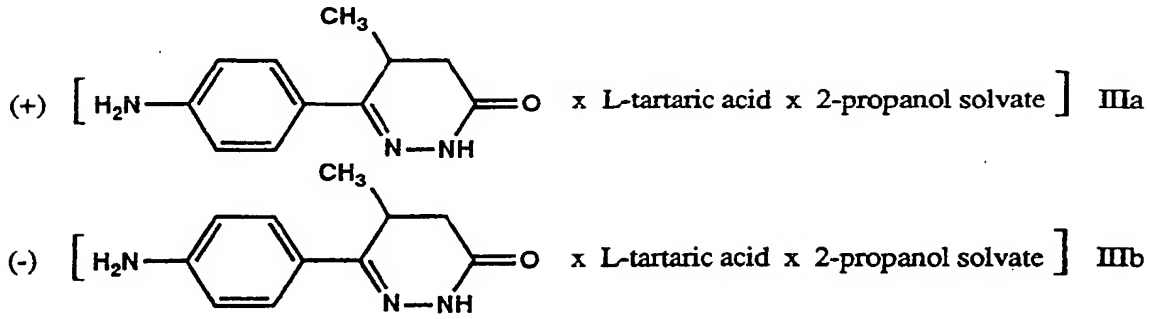
5. A process as claimed in claim 3 or 4, wherein the L- or D-tartaric acid is used in an amount of from about 2 to about 3 equivalents of acid per equivalent of enantiomers.

6. A process as claimed in claim 3, 4 or 5, wherein the crystalline salt comprises diastereomeric intermediate salt of formulae (IIIa) or (IIIb)



7. A process for preparing optically substantially pure (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or (+)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-propanedinitrile which comprises treating optically substantially pure (-) or (+) enantiomer of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one prepared according to any of claims 3-6 with sodium nitrite and malononitrile.

8. Diastereomeric intermediate salts of formulae (IIIa) or (IIIb)



9. A method for treating congestive heart failure in a mammalian organism, said method comprising administering an effective amount to treat congestive heart failure of a compound as claimed in claim 1 to a mammalian organism in need of such treatment.

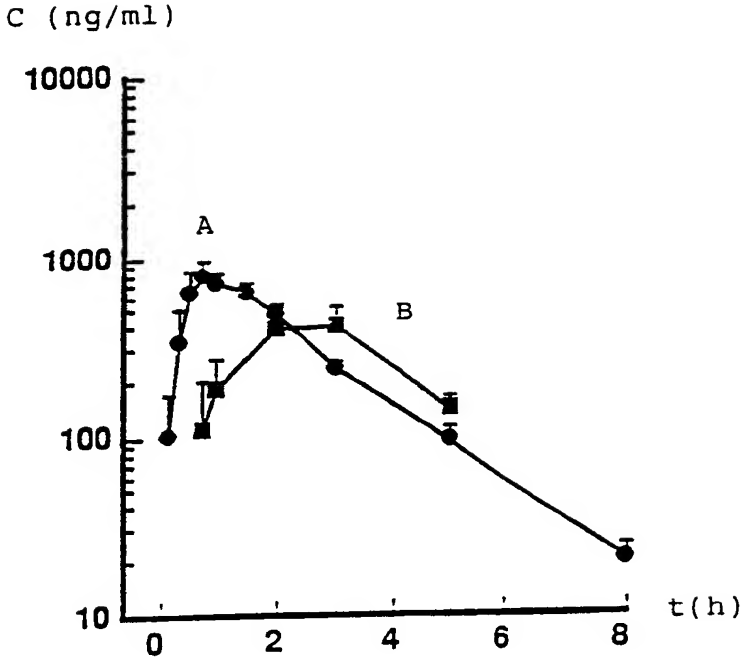


FIGURE 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 92/00003

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)°

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 237/04 A 61 K 31/50

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 237/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0259835 (TEIKOKU HORMONE) 16 March 1988, see claims 1,5,7,8,9; pages 25-27 ---	1,2,7
P,A	EP,B,0208518 (SMITH KLINE) 14 January 1987, see claims 1,11,12,15,17; pages 17-20 (cited in the application) ---	1,2,7
A	US,A,4521415 (KATAKAMI et al.) 4 June 1985, see claims 1,17-22 ---	1,2
A	US,A,4843072 (YASUDA et al.) 27 June 1989, see claims 1,5 ---	1,2
A	US,A,4914093 (MORISAWA et al.) 3 April 1990, see claim 1; abstract ---	1,2
A	GB,A,2228004 (ORION) 15 August 1990, see claims 1,22 (cited in the application) -----	1,2

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-03-1992	15 APR 1992
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 9, because they relate to subject matter not required to be searched by this Authority, namely:

see PCT rule 39.1(iv)
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. [ ] Claim numbers ____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. FI 9200003 SA 54729

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 09/04/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP-A,B 0259835	16-03-88
		JP-A- 63183568	28-07-88
US-A- 4914093	03-04-90	JP-A- 61093169	12-05-86
		EP-A,B 0178189	16-04-86
		EP-A- 0330242	30-08-89
GB-A- 2228004	15-08-90	AU-B- 619648	30-01-92
		AU-A- 4929690	16-08-90
		EP-A- 0383449	22-08-90
		JP-A- 2288868	28-11-90
		US-A- 5019575	28-05-91

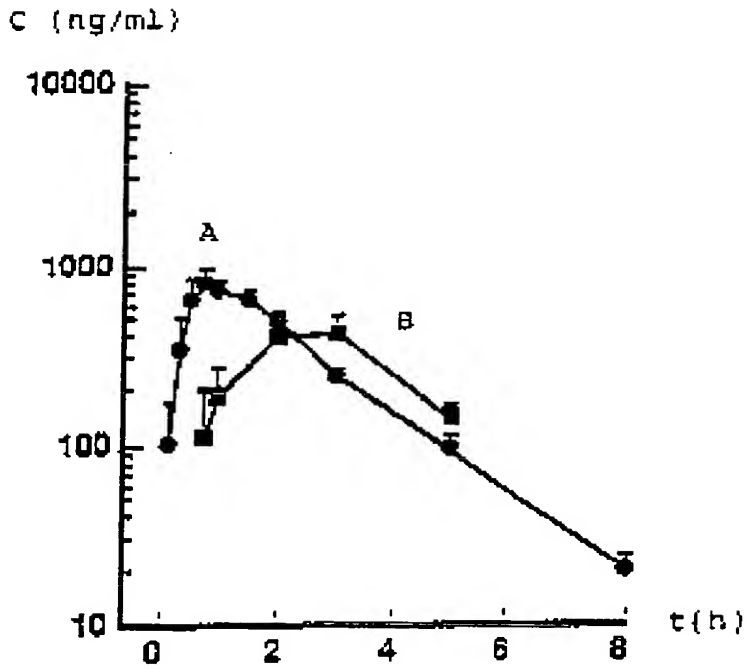

FIGURE 1.